AMENDMENT OF CLAIMS

Please cancel Claims 57, 58 and 76-79, and amend Claims 34, 35, 46, 50, 59-64 and 66 as follows:

30. (Previously added) A soluble proteic fragment of a subtilisin-kexin isoenzyme named SKI-1 which has the amino acid sequence defined by amino acids 187 to 996 of any one of SEQ ID NOs: 2, 4, and 6, and a variant thereof, which is enzymatically active.

31. (Previously added) A proteic fragment of a subtilisin-kexin isoenzyme named SKI-1, which has the amino acid sequence defined by amino acids 18 to 137 of any one of SEQ ID NOs: 2, 4 and 6, and a variant thereof, which is capable of binding with amino acids 18 to 1052 of SKI-1 in whole or in part.

32. (Previously added) The proteic fragment of claim 31, wherein said part has a molecular weight of about 14 Kda and forms a tight complex with the soluble fragment of SKI-1.

33. (Previously added) The proteic fragment of claim 31, which is an inhibitor of SKI-1 activity.

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34. (Currently amended) The proteic fragment of claim 33, wherein the SKI-1 amino acid sequence ~~that~~ is modified to prevent further enzymatic processing in a cell expressing said protein fragment.

35. (Currently amended) The proteic fragment of claim 34, wherein the SKI-1 amino acid sequence ~~which~~ is modified by amino acid substitution, deletion or rearrangement.

36. (Previously added) An isolated nucleic acid encoding a protein fragment as defined in claim 30.

37. (Previously added) An isolated nucleic acid encoding a proteic fragment as defined in claim 31.

38. (Previously added) An isolated nucleic acid encoding a proteic fragment as defined in claim 32.

39. (Previously added) An isolated nucleic acid encoding a proteic fragment as defined in claim 33.

40. (Previously added) A recombinant vector comprising the nucleic acid defined in claim 36.

41. (Previously added) The recombinant vector of claim 40, which is an expression vector.

42. (Previously added) The recombinant vector of claim 41, which comprises a promoter expressible in a target cell wherein expression of said nucleic acid is desirable.

43. (Previously added) The recombinant vector of claim 42, which comprises an inducible promoter.

44. (Previously added) A recombinant host cell comprising the recombinant vector defined in claim 40.

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45. (Previously added) A method of producing a proteic fragment of SKI-1 enzyme, which comprises the steps of:

culturing a recombinant host cell expressing a nucleic acid as defined in claim 36 in a cell growth and expression-supportive culture medium; and recovering said protein fragment of SKI-1 in the culture medium.

46. (Currently amended) A method for cleaving a substrate for SKI-1 enzyme, which comprises the step of:

a) contacting said substrate with a SKI-1 enzyme which has 1) an amino acid sequence defined by amino acids 18 to 1052 of any one of SEQ ID Nos: 2, 4, 6 and an active variant thereof, or 2) a SKI-1 soluble fragment of a subtilisin-kexin isoenzyme named SKI-1 which has the amino acid sequence defined by amino acids 187 to 996 of any one of SEQ ID

NOs: 2, 4, and 6, and a variant thereof, which is enzymatically active, or 3) catalytic part of a) or b), or 4) a complex as defined in claim 32, for a time sufficient and in conditions adequate for such cleavage to occur,

with the proviso that said substrate is not a sterol-regulatory element-binding protein (SREBP).

47. (Previously added) A method for producing a protein or a peptide from a proteic precursor which is an enzymatic substrate for SKI-1 enzyme, which comprises the steps of:

a) contacting said proteic precursor with a SKI-1 enzyme which has 1) an amino acid sequence defined by amino acids 18 to 1052 of any one of SEQ ID Nos: 2, 4, 6 and an active variant thereof, or 2) a SKI-1 soluble fragment of a subtilisin-kexin isoenzyme named SKI-1 which has the amino acid sequence defined by amino acids 187 to 996 of any one of SEQ ID NOs: 2, 4, and 6, and a variant thereof, which is enzymatically active, or 3) a catalytic part of a) or b), or 4) a complex as defined in claim 32, for a time sufficient and in conditions adequate for such cleavage to occur; and

b) recovering said protein or peptide;

with the proviso that said substrate is not a sterol-regulatory element-binding protein (SREBP).

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48. (Previously added) The method of claim 47, which takes place in a cell or in the presence of a cellular population and wherein step a) comprises the step of transfecting a cell with a nucleic acid expressing said SKI-1 enzyme.

49. (Previously added) The method of claim 48, wherein said cell expresses said proteic precursor or is transfected with a nucleic acid expressing said proteic precursor.

50. (Currently amended) A method of inhibiting the activity of a subtilisin-kexin isoenzyme named SKI-1, which comprises the step of contacting SKI-1 with the inhibitor of claim 33 or isolated nucleic acid encoding the inhibitor.

51. (Previously added) A peptide of at least 7 amino acids capable of binding to and of being cleaved by SKI-1 catalytic site, comprising the following general formula:

$$\text{Arg } Xaa_1 \text{ J}Xaa_2 \downarrow Xaa_3 (Z)_nO$$

wherein $Xaa_{1, 2, 3}$ and Z are any amino acid

J is an alkyl or aromatic hydrophobic amino acid

N is 1, 2 or 3

O is an acidic amino acid,

with the proviso that the peptide does not comprise the sequence Lys-Arg-Phe-Val-Phe-Asn-Lys-Ile-Glu.

52. (Previously added) A peptide as defined in claim 51, wherein Xaa_2 is Lys, Leu, Phe or Thr.

53. (Previously added) A peptide as defined in claim 52 which has the sequence: H_2N-Val-Phe-Arg-Ser-Leu-Lys-Tyr-Ala-Glu-Ser-Asp-COOH.

54. (Previously added) A peptide as defined in claim 51 which is labelled.

55. (Previously added) A peptide as defined in claim 54 which is fluorogenic.

56. (Previously added) A peptide as defined in claim 55 which is

Abz-Val-Phe-Arg-Ser-Leu-Lys-Tyr-Ala-Glu-Ser-Asp-Tyr(NO_2),

wherein

Abz is orthoaminobenzoic acid, and

Tyr(NO_2) is 3-nitrotyrosine.

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57-58. (Cancelled)

59. (Currently amended) A method for screening for a polypeptide that has the activity of ~~The use as defined in claim 51 for screening~~ a subtilisin-kexin isoenzyme named SKI-1, the method comprising the steps of:

contacting the peptide of claim 51 to a test polypeptide under conditions that allow cleavage of the peptide by a SKI-1; and

detecting the cleavage of the peptide wherein the presence of the cleavage indicates that the polypeptide has SKI-1 activity.

60. (Currently amended) A method for monitoring the activity of a subtilisin-kexin isoenzyme named SKI-1 comprising the steps of ~~The use of a peptide of at least 7 amino acids capable of binding to and of being cleaved by SKI-1 catalytic site, comprising the following general formula~~:

contacting a sample having or suspected of having SKI-1 activity with the peptide of claim 51; and

monitoring the cleavage of the peptide.

~~Arg Xaa_1 JXaa$_2$ ↓ Xaa_3 $(Z)_n$O~~

~~wherein $Xaa_{1, 2, 3}$ and Z are any amino acid~~

~~J is an alkyl or aromatic hydrophobic amino acid~~

~~N is 1, 2 or 3~~

~~O is an acidic amino acid,~~

~~for monitoring the activity of a subtilisin-kexin isoenzyme named SKI-1~~.

61. (Currently amended) A method for screening inhibitors or substrates of a subtilisin-kexin isoenzyme named SKI-1 comprising the steps of ~~The use of a peptide of at least 7 amino acids capable of binding to and of being cleaved by SKI-1 catalytic site, comprising the following general formula~~:

contacting a protein which has SKI-1 activity with the peptide of claim 51 in the presence of a test compound under the conditions that allow the cleavage of the peptide by the protein with SKI-1 activity;

determining the cleavage of the peptide; and

comparing the cleavage of the peptide with that of a control group in which the protein with SKI-1 activity is contacted with the peptide of claim 51 in the absence of the test compound under the same conditions wherein a lower than control cleavage rate indicates that the test compound is an inhibitor or substrate of SKI-1.

~~Arg Xaa_1 JXaa$_2$ ↓ Xaa_3 $(Z)_n$O~~

~~wherein $Xaa_{1, 2, 3}$ and Z are any amino acid~~

~~J is an alkyl or aromatic hydrophobic amino acid~~

~~N is 1, 2 or 3~~

~~O is an acidic amino acid,~~

~~for screening inhibitors or substrates of a subtilisin-kexin isoenzyme named SKI-1.~~

62. (Currently amended) A method ~~The use of an inhibitor of the activity of a subtilisin-kexin isoenzyme named SKI-1 in the making of a medication~~ for treating a disease ~~involving~~ related to an overexpression of a subtilisin-kexin isoenzyme named SKI-1 or a SKI-1 substrate in a human or non-human animal, the method comprising the step of:

administering to the human or non-human animal an inhibitor of the activity of SKI-1 in an amount sufficient to inhibit the activity.

63. (Currently amended) The method of ~~use as defined in~~ claim 62, wherein said disease is associated with any one of hypercholesterolemia, high levels of fatty acids, lipids or farnesyl pyrophosphate, liver steatosis, Ras-dependent cancer, restenosis and amyloid protein formation.

64. (Currently amended) The method of ~~use as defined in~~ claim 62, wherein said inhibitor is defined in claim 31.

65. (Previously added) A composition comprising a SKI-1 fragment as defined in claim 30.

66. (Currently amended) A method for cleaving a proteic precursor which is SKI-1 substrate, the method comprising the steps of: providing ~~The use of~~ a SKI-1 enzyme as encoded by a nucleic acids having a nucleotide sequence of nucleotides 469 to 3573 ~~to 18 to 1052~~ of SEQ ID NO~~s~~: 1, nucleotides 59 to 3163 of SEQ ID NO:3 or nucleotides 548 to 3652 of SEQ ID NO:5, ~~or of~~ a catalytic part of SKI-1 that is unique to SKI-1 enzyme and encoded by the corresponding sequence on SEQ ID NOs: 1, 3 or 5, or ~~of~~ an active variant of the SKI-1 enzyme or the catalytic part ~~thereof~~, wherein the nucleotide sequence that encodes the variant shares ~~nucleic acid of the variant sharing~~ at least 70% homology with a nucleotide sequence on ~~nucleic defined in~~ SEQ ID NOs: 1, 3 ~~and~~ or 5 and hybridize to SEQ ID NOs: 1, 3 or 5 ~~hybridizing therewith~~ under stringent hybridization conditions;~~, for cleaving a proteic precursor,~~ and contacting the proteic precursor with the SKI-1 enzyme, the catalytic part of SKI-1, or the active variant of the SKI-1 enzyme or the catalytic part under conditions that allow the cleavage of the proteic precursor, with the proviso that said proteic precursor is not a sterol-regulatory element-binding protein (SREBP).

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67. (Previously added) A composition comprising an SKI-1 fragment as defined in claim 31.

68. (Previously added) A composition comprising a SKI-1 fragment as defined in claim 32.

69. (Previously added) A composition comprising a SKI-1 fragment as defined in claim 33.

70. (Previously added) A composition comprising a SKI-1 fragment as defined in claim 34.

71. (Previously added) A composition comprising a SKI-1 fragment as defined in claim 35.

72. (Previously added) A composition comprising a nucleic acid as defined in claim 36.

73. (Previously added) A composition comprising a nucleic acid as defined in claim 37.

74. (Previously added) A composition comprising a nucleic acid as defined in claim 38.

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75. (Previously added) A composition comprising a nucleic acid as defined in claim 39.

76-79. (Cancelled)

80. (Previously added) A composition comprising a recombinant vector as defined in claim 40.

81. (Previously added) A composition comprising a recombinant vector as defined in claim 41.

82. (Previously added) A composition comprising a recombinant vector as defined in claim 42.

83. (Previously added) A composition comprising a recombinant vector as defined in claim 43.